Reporting of Computational Modeling Studies in Medical Device Submissions

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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For questions regarding this document, contact Tina M. Morrison, Ph.D., (301) 796-6310, tina.morrison@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Office of Science and Engineering Laboratories

Preface

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Reporting of Computational Modeling Studies in Medical Device Submissions

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Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

Introduction

For many years, computational modeling and simulation (CM&S) studies have been used by sponsors as a tool to support medical device applications. These studies have traditionally been used in the areas of fluid dynamics (e.g., shear stress and stagnation calculations in ventricular assist devices), solid mechanics (e.g., maximum stress locations in a hip implant), electromagnetics and optics (e.g., radiofrequency dosimetry in magnetic resonance imaging, fluence for fiber optic spectroscopy devices), ultrasound propagation (e.g., absorbed energy distribution for therapeutic ultrasound), and thermal propagation (e.g., radiofrequency and laser ablation devices). The purpose of this guidance document is to provide recommendations to industry on the formatting, organization, and content of reports of CM&S studies that are used as valid scientific evidence to support medical device submissions. Moreover, this guidance is also for FDA Staff, to help improve the consistency and predictability of the review of computational modeling and simulation studies and to better facilitate full interpretation and complete review of those studies.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Scope

Computational modeling and simulation studies, together with bench, non-clinical *in vivo*, and clinical studies, are tools that can be used to evaluate the safety and effectiveness of medical devices. In order for the CM&S studies to provide valid scientific evidence in regulatory submission, specific details need to be included in the report of the studies. In this guidance, the term "CM&S report" refers to the part of a premarket submission that provides information about a CM&S study; the term does not describe a new submission requirement.

The outline provided in this document aims to establish uniformity in reporting CM&S studies. FDA recognizes that there is a variety of CM&S modalities and specific details will vary across disciplines. Therefore, we have provided a general outline in the main body of this document and five subject matter appendices for modeling and simulation modalities that are widely used in regulatory submissions. The main body is written in general terms to capture reporting for any modality. The five appendices provide more background, structure, and specific terminology for the following subject areas:

I. Fluid Dynamics and Mass Transport
II. Solid Mechanics
III. Electromagnetics and Optics
IV. Ultrasound
V. Heat Transfer

For multiphysics modeling, recommendations in several of these appendices may apply.

Apart from the CM&S being used to support regulatory submission, we recognize that CM&S can be part of a medical device (e.g., physiological closed-loop feedback system for ventilator), or can be the medical device (e.g., electrical source estimation software, standalone medical device intended to provide decision support). This guidance document does not address the reporting of the latter two uses of CM&S, though the overall concepts outlined in this guidance are applicable.

While verification and validation are necessary components of the report of CM&S studies, this document does not establish levels of verification and validation needed for regulatory submissions. Further, this guidance document does not address how to conduct a computational modeling or simulation study, nor does adherence to this guidance ensure that your computational modeling or simulation study is adequate or appropriate. This guidance only provides guidelines for reporting this information to FDA and highlights some common issues with models and simulations.

Outline of the CM&S Report

In the following section, we provide the recommended headings and details for a CM&S report contained within a premarket submission.

I. Executive Report Summary

We recommend that you provide a concise and complete overview of the report of the computational modeling and/or simulation study, which includes the following:

- Context of use of analysis (e.g., to determine the maximum stress location)

- Type of analysis (e.g., fluid dynamics and mass transport, solid mechanics, electromagnetics and optics, ultrasound, heat transfer)
- Scope of the analysis (e.g., for a device that has multiple sizes and/or configurations, discuss which sizes and/or configurations were modeled, and how the computational model relates to the intended patient population)
- Conclusions with respect to the study context of use and how they relate to the regulatory submission
- Keywords – we recommend that you provide up to five keywords or key phrases that describe the modeling modality, the device product code[1], any relevant materials of the device, analysis type, and if applicable, location in the body for intended use. For example, you could provide the key words in the following format:
    - finite element analysis, MIH, nitinol, fatigue, aorta;
    - radiofrequency dosimetry, OQG, cobalt chromium, magnetic resonance safety, hip.

II. Background/Introduction

We recommend that you provide a brief description of the device system and intended use environment. Discuss the context of use analysis, as this will dictate the relevant details necessary for review.

III. System Configuration

We recommend that you provide information regarding the system configuration (e.g., the geometry of the device, the computational domain, the structure of a physiological control system, the *in vitro* test that is modeled).

A. Details

Describe the components of the system (e.g., device, *in vivo* and/or *in vitro* environment) to be evaluated. Include images, diagrams (with appropriate scaling bar or dimensions), and a brief description of the model.

Describe the methods (e.g., image reconstruction, computer aided design (CAD)) used to generate the system configuration and discuss how the configuration was appropriately captured for the intended analysis.

Describe the software used to generate the system configuration (e.g., CAD software, image segmentation software, control-system simulation software). State whether the software is commercially available, and if not, describe the methods used to verify the software. If image reconstruction was used to generate geometry, describe the imaging modality.

[1] For more information, please see the FDA guidance *Medical Device Classification Product Codes* issued on April 11, 2013; http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm285317.htm.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications used to generate the system configuration as compared to the actual device and environment. If appropriate, provide a clinical rationale for the *in vivo*/*in vitro* models (e.g., size, disease state, mathematical convenience versus clinical relevance).

IV. Governing Equations/Constitutive Laws

We recommend that you provide information regarding the governing equations and/or constitutive laws used to perform the computational analysis.

A. Details

Provide the governing equations/constitutive laws for the system.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications of the governing equations/constitutive laws chosen to represent the system.

V. System Properties

We recommend that you provide information regarding the biological, chemical, and physical properties of the system.

A. Details

Describe all system properties used in the analysis. These might include biological materials (e.g., cells, tissues, organs) and/or processes (e.g., cell signals), and/or states (e.g., diseased, healthy), chemical properties, and physical properties that define the materials and/or process characteristics. Provide the parameters that define the material characteristics (e.g., biological, physical, chemical), and their variability, if applicable.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications used to determine the system properties. Identify the source of biological, chemical, and physical properties (e.g., literature, *in vivo*, *ex vivo*, *in vitro* testing).

VI. System Conditions

We recommend that you provide information regarding the conditions that were imposed on the system. These might include, but are not limited to, the boundary and loading conditions, initial conditions, and other constraints that control the system.

A. Details

Describe the system conditions imposed on the model and their variability, if applicable. If appropriate, provide a graphical representation of the conditions, depicting how they are applied to the system.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications used to determine the conditions applied on the system. Provide appropriate documentation (e.g., literature, test reports, clinical data, medical imaging data).

VII. System Discretization

We recommend that you provide information regarding the discretization and refinement techniques applied to the system for solving it numerically.

A. Details

Describe the system discretization methods and how they were applied to the computational domain. Describe the methodology (e.g., mesh refinement study) used to verify suitably resolved computational domain. If applicable, provide a representative image of the discretization in the areas of interest of the computational domain. Report the criteria used to determine that the discretization was sufficient to resolve the physics of interest.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications used to discretize the computational domain.

VIII. Numerical Implementation

We recommend that you provide information regarding the numerical implementation strategy that yielded the solution to the governing equations.

A. Details

Describe the numerical implementation methodology and/or numerical solver employed to yield the solution to the governing equation. Explain the verification process used to ensure the governing equations were solved correctly. State the solver parameters (e.g., tolerance, relaxation) and convergence criteria.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications used to determine the solver and associated parameters.

IX. Validation

We recommend that you provide information regarding the methods employed to validate the computational model.

A. Details

Describe the method used to assess the accuracy of the computational model (e.g., *in vivo*, *ex vivo* or *in vitro* comparator). Provide sufficient details that describe how the measurements were taken from the comparator and used to assess the accuracy of the numerical output.

B. Assumptions, simplifications, and rationale

Describe and provide the rationale for the assumptions and simplifications of the method (e.g., *in vivo*, *ex vivo* or *in vitro* test) used to validate the computational model. Explain the difference between the measured and model values, and discuss its significance with respect to the purpose of the analysis.

X. Results

We recommend that you present the quantitative results from the computational modeling study. Provide the results with sufficient level of details, including labels and legends. The results may be presented in more than one format (e.g., table, graph, plot).

XI. Discussion

We recommend that you discuss how the results from the modeling study relate to the context of use, and if appropriate, the clinical relevance and how the results compare with experimental and literature results.

XII. Limitations

We recommend that you provide details regarding how the assumptions/simplifications described in the previous sections might affect the output of the computational model, the interpretation of the results, and the relevance to the purpose of the study. Describe the outcomes and implications of all the available uncertainty analyses performed on the system properties and conditions.

XIII. Conclusions

We recommend that you summarize the computational study with respect to the purpose of the study and how the study relates to the regulatory submission.

Glossary

We have provided the following definitions to explain the terminology used in this guidance document.

Accuracy: the difference between a parameter, variable or derived quantity (or a set of parameters or variables) within a model, simulation, or experiment and the true value or the assumed true value.

Analysis: any post-processing or interpretation of the individual values, arrays, files of data, or suites of executions resulting from a simulation.

Computational model: the numerical implementation of the mathematical model performed by a means of a computer.

Constitutive law: an expression which describes the relationship between biological, chemical or physical quantities for a specific material or substance under external stimuli (e.g., Hooke's Law).

Context of use: the purpose or intended use of the computational model and/or simulation study.

Convergence analysis: the process of ensuring the solution resolves the physics of interest and the variation of the solution remains within a pre-specified range as the discretization is refined.

Governing equation: the mathematical relationship that describes the phenomena of interest.

Mathematical model: the mathematical equations, boundary values, initial conditions, and modeling data needed to describe the conceptual model.

Model: a description or representation of a system, entity, phenomena, or process (adapted from Banks, J., ed. (1998). Handbook of Simulation. New York: John Wiley & Sons). Any data that go into a model are considered part of the model. Models may be mathematical, physical, or logical representations of a system, entity, phenomenon, or process. Models can be used by simulation to predict a future state, if so desired.

Simulation: the imitation of the characteristics of a system, entity, phenomena, or process using a computational model.

Subject matter: a particular technical discipline, system, or process regarding computational modeling methodologies.

System discretization: the division of the computational domain of the system into discrete parts for numerical implementation.

Uncertainty: the estimated amount or percentage by which an observed or calculated value may differ from the true value (The American Heritage Dictionary of the English Language, 4th ed.).

Validation: The process of determining the degree to which a model or a simulation is an accurate representation of the real world from the perspective of the intended uses of the model or the simulation (American Society of Mechanical Engineering Verification &Validation Guide – ASME V&V 10-1-2012).

Verification: The process of determining that a computational model accurately represents the underlying mathematical model and its solution from the perspective of the intended uses of modeling and simulation (American Society of Mechanical Engineering Verification &Validation Standard – ASME V&V 20-2009).

Subject Matter Appendix I – Computational Fluid Dynamics and Mass Transport

For questions regarding this appendix, contact Sandy Stewart, Ph.D., (301) 796-2581, sandy.stewart@fda.hhs.gov.

Introduction/Scope of the Appendix

The purpose of this appendix is to provide recommendations on the formatting, organization, and content of reports for computational fluid mechanics and mass transport modeling and simulation studies in medical device regulatory submissions. Moreover, this guidance is for FDA Staff, to help improve the consistency and predictability of the review of computational modeling studies and to better facilitate full interpretation and complete review of those studies.

Specific examples provided in this appendix, such as output metrics, are only examples and should not be considered as requirements or recommendations for the type of validation to complete.

Outline of the Report

In the following section, we provide an outline for reporting the details of your computational modeling and simulation study.

I. Executive Report Summary

We recommend that you provide a concise and complete overview of the report of the computational modeling and/or simulation study, which includes the following:

- Briefly summarize the purpose and scope of the analysis, as well as the rationale for choosing the modeling approach as opposed to other approaches (e.g., experiment).
- Briefly summarize the type(s) of analysis(es) conducted in the computational modeling study (e.g., fluid mechanics, diffusion, diffusion/convection).
- Briefly summarize the model, including geometry, material properties, and boundary/initial conditions.
- If the device has multiple sizes and/or configurations, provide a rationale for the sizes and configurations of the device system evaluated and not evaluated.
- State whether the analysis code/software is commercially available, open source, or user developed.

- Discuss the simulation results (and experimental validation) and their implications for device safety and effectiveness. If applicable, discuss the simulation results with respect to bench testing results.
- Summarize the limitations.
- Summarize the conclusion(s).
- Keywords – please provide up to five keywords or key phrases that describe the modeling modality, the device product code, any relevant materials of the device, analysis type and if applicable, location in the body for intended use (e.g., computational fluid dynamics, NIQ, stainless steel, drug transport, coronary artery). For example, the following are sample keywords relevant to this subject matter:
  - biofluid mechanics, drug delivery, blood flow, transport, finite volume method, finite element method, pump.

II. Background/Introduction

We recommend that you state the purpose and scope of the analysis, as this will determine the relevant details necessary for review. Provide a brief description of the device, along with its intended use environment and deployment/implantation procedure. The details provided in this section should correspond to the objectives of the analysis.

III. System Geometry (System Configuration)

We recommend that you provide information regarding the system configuration (e.g., the geometry of the device, the computational domain, the structure of a physiological control system, the *in vitro* test that is modeled).

A. Details

We recommend that you describe the components of the system (e.g., device, vessel, organ, organ system) to be evaluated. Provide all relevant dimensions of the device and geometry. Include diagrams, schematics, and photos as needed.

Describe methods/ software (e.g., image reconstruction, CAD) used to generate the geometry in order to demonstrate that the configuration was captured appropriately for the intended analysis. In particular, describe any scaling or similarities (e.g., geometric and dynamic similarity).

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications used to generate the system configuration as compared to the actual device and environment.

For example, if the entire device system was not modeled or if simplifications were made to the geometry, provide a rationale for the system geometry that was analyzed (e.g., the use of symmetry, only a portion of device, or representative inlet and outlet geometries), including the following:

- Describe any differences between the model and the actual configuration.

- Discuss how manufacturing tolerance dimensions influence the results compared to nominal dimensions.
- Describe how the inlet and outlet geometries were selected and how these might affect the flow regime.
- If the device has unique geometric features (e.g. surface topography) that might affect the analysis, then describe how those were or were not accounted for in the model.
- Include relevant information on limitations and assumptions (e.g., scaling) image resolution, smoothing, image segmentation errors, as related to the geometry.

IV. Governing Equations/Constitutive Laws

We recommend that you provide information regarding the governing equations and/or constitutive laws used to perform the computational analysis.

A. Details

Provide the governing equations/constitutive laws for the system, including the following:

- describe the equations defining the model (e.g., Navier-Stokes equations for fluid flow, Fick's equations for diffusion, Darcy's equations for porous flow);
- describe the constitutive relationships used in the simulation (e.g., the relation between shear stress and velocity gradient for fluid flow, the relation between diffusion flux and concentration gradient for diffusive flow, the relation between discharge flux and pressure gradient for porous flow);
- describe the turbulence modeling used, if any, including any specialized wall functions used; and
- describe any other specialized mathematical modeling used (e.g., blood damage modeling).

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications of the governing equations and constitutive laws chosen to represent the system, including the following:

- describe the simplifications of the basic mathematical equations based on assumptions and rationale (purpose) of the simulation being undertaken;
- describe the assumptions and rationale involved in simplifying the governing equations (e.g., use of steady rather than unsteady flow);
- provide information that confirms that the constitutive model(s) captures the actual behavior being modeled; and
- provide a rationale for the use of any turbulence model or wall functions, as well as other equations used to capture additional phenomena (e.g., blood damage models).

V. System Properties

We recommend that you provide information regarding the biological, chemical, and physical properties of the system.

A. Details

Provide, preferably in a tabular form, all physical properties, coefficients, and descriptive equations used in the simulation and post processing, such as:

- fluid viscosity and density
- gas solubility and diffusivity
- diffusion and reaction coefficients of constituents
- permeability and porosity
- temperature dependence of properties if the simulation is not isothermal

Provide a report of any testing conducted to generate the system properties, if available.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications used to determine the system properties. Identify the sources of the physical properties and coefficients adopted (e.g., literature, *in vivo*, *ex vivo*, *in vitro* testing). If literature data are cited, discuss their applicability to the specific conditions. If testing is conducted to determine the parameters, then provide details regarding the test. If applicable, discuss any relevant aspects of tissue physiology used in the model (e.g., young versus mature, healthy versus diseased).

If there are uncertainties associated with the data (e.g., due to inaccuracies, simplifications, or variations), describe the sensitivity analysis you performed, if appropriate, to address the effect of the uncertainties on the simulation results.

VI. Boundary and Initial Conditions (System Conditions)

We recommend that you provide information regarding the conditions that were imposed on the system. These might include, but are not limited to, the boundary and loading conditions, initial conditions, and other constraints that control the system.

A. Details

Describe the boundary conditions (e.g., inlet and outlet, walls) of the model. Describe any global boundary conditions used to represent the simulation in global terms (e.g., pressure drop, mass flow rates, revolutions per minute).

If the model was time dependent, provide the following:

- state the initial conditions;
- if applicable, describe changing boundary conditions as a function of time (e.g., function, table);
- if the model was pulsatile, provide the number of initial cycles modeled to damp out initial transient effects, if any;

- describe how time steps were determined and were deemed appropriate for the analysis (e.g., time step refinement study); and
- describe any unsteady model(s) employed as an adjunct to a steady model using a rotating or moving frame of reference (e.g., for blood pump).

Provide any relevant nondimensional numbers, such as:

- Reynolds number
- Strouhal or Womersley number (pulsatile flows)
- Peclet or Sherwood number (diffusion/convection)
- Dean number (curved flow)

If symmetry was used to reduce the size of the model, then describe the symmetry boundary conditions.

If a turbulence model was used, then provide the turbulence boundary conditions.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications used to determine the conditions applied on the system. Provide appropriate documentation the system conditions (e.g., literature, test reports, clinical data, medical imaging data).

In particular, describe any differences or simplifications between the simulation environment and the actual environment, such as,

- choice of boundary conditions used;
- operating conditions of the simulation, especially if the simulation did not cover the expected range of use of the device; and
- other simplifications (e.g., use of symmetry, rotating frame of reference instead of unsteady simulation for centrifugal pump).

VII. System Discretization

We recommend that you provide information regarding the discretization and refinement techniques applied to the system for solving it numerically as outlined below.

A. Details

Provide the following regarding the mesh:

- Describe the software used for generating the mesh.
- Describe the mesh in all regions of the computational domain (e.g., device, fluid, surrounding tissue).
- Describe and provide a rationale for the quality of the mesh (e.g., element/cell types, sizes, shapes, quality metrics (i.e., aspect ratios)).
- Discuss areas of local mesh refinement in areas of interest (e.g., areas of high shear stress, recirculation zones, critical concentrations, interactions between the device and the body) and provide representative images of the mesh in these areas.

- Describe any special elements/cells used if a turbulence model (or any other numerical method requiring special elements/cells) was used.

B. Assumptions, simplifications, and rationale

Provide the following regarding the mesh refinement study that supports the mesh:

- Describe any adaptive meshing or automatic mesh refinement used.
- Describe the mesh refinement study, and provide representative images of the meshes used in the refinement study.
- Discuss how the mesh sensitivity analysis was performed to justify the production mesh used for the subsequent simulations, that is, to demonstrate that the mesh density did not affect the numerical results.
- Provide a rationale for the numerical metrics (e.g., shear rates, concentration gradients) chosen to establish the mesh density.
- Provide a rationale for the algorithm for assigning the mesh density or distribution.

VIII. Numerical Implementation

We recommend that you provide information regarding the numerical implementation strategy that yielded the solution to the governing equations.

A. Details

Describe the discretization of the equations, including:

- numerical method used (e.g., finite element, finite volume, finite difference);
- temporal discretization, if any (e.g., explicit, implicit, semi-implicit);
- spatial discretization (i.e., interpolation of field variables between grid points); and
- method for interpolating from face to nodes or vice versa (e.g., upwind, power law).

Describe the solution methods and provide the following:

- solver method (e.g., Newton, multigrid);
- solver parameters (e.g., linear solver and tolerance, preconditioners, analytic or numerical Jacobian);
- type of software (e.g., commercial, open-source, user-developed) and name, if applicable;
- user-supplied subroutines/code; and
- convergence criteria (e.g., error method, error threshold, sampling locations and variables used).

Describe the code verification and provide the following:

- comparisons to simplified systems which have an analytical solution; and
- sensitivity analyses of the discretization scheme and solver parameters performed using the actual system (e.g., timestep, gridsize (grid refinement) and convergence criteria (e.g., 1E 6 vs 1E 7)).

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications used to determine the solver and associated parameters. For example, provide a rationale for the discretization/solver choices made (i.e., benefits over other choices) and discuss the ramifications of the particular choice (i.e., discretization errors).

IX. Validation

We recommend that you provide information regarding the methods employed to validate the computational model [1]. We recommend the following format for presenting that information.

A. General Description
- Describe, if any, the experimental or analytical comparator that was used for model validation study (e.g., velocity, wall shear stress calculations, hydrodynamic pressure loss). If a comparator was used, describe if the comparison was made in a quantitative (preferred) or qualitative manner.
- Describe experimental uncertainty estimates if an experimental comparison is performed.

B. Methods
- Describe the validation test conditions and geometry.
- Describe the region of interest where validation(s) are performed.
- Provide diagrams and data to support the assessment of the model.
- Describe instrumentation and calibration.
- If a biological process was modeled (e.g., hemolysis, platelet damage, binding of drug in vessel tissue), then describe how the biological calculations were verified and validated.

C. Assumptions and Rationale
- Describe any simplifications for experimental comparator (e.g., use of surrogates when biological information is lacking).
- Provide a rationale to support any differences between the operating and boundary conditions of the comparator experiments and simulations.
- Provide a rationale for any geometric and dynamic scaling assumptions.

D. Validation Study Results
- Provide qualitative comparisons between your computational model output and experimental results. For example, images that directly compare model and experimental results (e.g., velocity or shear stress) can provide an overall qualitative assessment of how well the model can capture relevant behavior.
- Provide quantitative comparisons for critical areas of relevance to the goals of the study [2, 3].

E. Discussion
- Discuss the degree of agreement between the computational and experimental results.
- Discuss the relevance of your validation experiment to expected clinical loading conditions, implications of model and experimental assumptions on the results, limitations on the agreement between the validation model and

experiment, and the extent of predictability to your device or device-tissue model.
- If predictions of behavior are given in areas that are not accessible by experiment, provide a measure of confidence.

X. Results

We recommend that you present the quantitative results from the computational modeling study. Provide the results with sufficient level of details, including labels and legends. The results may be presented in more than one format (e.g., table, graph, plot).

Specifically, we recommend that you present the results in regions of interest graphically and quantitatively. Additionally, please provide the following:
- a statement of biological and other formulations (e.g., hemolysis);
- a description of the results in relation to the goals of the study;
- a description of how the simulation numerically converged via residual reductions and/or monitoring of some physically relevant fluid flow quantity at a probe point or surface location;
- a method to demonstrate that the basic conservation laws were obeyed;
- a description of how the natural development and physical character of the flow was unaffected by the boundaries of the simulation;
- a description of any sensitivity analysis performed to determine how the solution varied as a function of parameters that are not well known (e.g., parameters contained in turbulence models, boundary conditions, fluid properties);
- if limited studies were performed, a statement that the worst-case was modeled and a description of that worst case;
- for biological extrapolations, a description of relevant variables (e.g., shear rates, exposure times, recirculation zones, drug concentrations);
- a description of any adverse effects of device flow on tissues or organs; and
- a description of acceptable performance factors based on the results.

XI. Limitations

We recommend that you provide details regarding how the assumptions/simplifications described in the previous sections might affect the output of the computational model and simulation, the interpretation of the results, and the relevance to the purpose of the study.

Because assumptions and simplifications are made in the generation of the model device, in the performance of the simulation, and in the interpretation of the analysis, it is important to describe the limitations of the use of the computational model and the interpretation of the results. Therefore, we recommend that you discuss how the assumptions/simplifications might affect the output of the model and simulation and the interpretation of its relevance to device performance and safety.

For example, it is important to know whether the simulation of blood flow through a small gap in a blood pump was based on the nominal dimensions or whether it includes the limits of the manufactured component tolerances. If you believe that your results are significantly dependent on the assumptions and/or simplifications in your model, you should consider performing sensitivity analyses on the computational model parameters associated with the assumptions and simplifications.

XII. Discussion/Conclusion

We recommend that you summarize the computational study with respect to the purpose of the study and how it relates to the regulatory submission (e.g., selecting the device size that is expected to perform the worst under the simulated use conditions, determining the safety factor under the clinically challenging scenario(s), establishing the loading conditions for bench testing). Discuss how the results compare with experimental results, literature results and/or prior product performances, if these results exist. Discuss the assumptions and simplifications that were made to the model and how they are expected to affect the results and interpretation of the results. Discuss the strength of your conclusions in terms of the limitations of the model that you have identified. Discuss how your results convey acceptable performance of the product *in vivo*, if applicable.

Bibliography

[1] ASME V&V20-2009, Standard for Verification and Validation in Computational Fluid Dynamics and Heat Transfer

[2] Oberkampf, W.L., Trucano, T.G., and Hirsch, C., 2004 “Verification, validation, and predictive capability in computational engineering and physics,” Applied Mechanics Reviews, 57, pp. 345–384.

[3] Oberkampf W.L. and Barone M.F., 2006 “Measures of agreement between computation and experiment: Validation metrics,” Journal of Computational Physics, 217, pp. 5-36.

Subject Matter Appendix II – Computational Solid Mechanics

For questions regarding this appendix, contact Jason Weaver, Ph.D., (301) 796-2504, jason.weaver@fda.hhs.gov.

Introduction/Scope of the Appendix

The purpose of this appendix is to provide recommendations on the formatting, organization, and content of reports for computational solid mechanics modeling studies in medical device regulatory submissions.

Specific examples provided in this appendix, such as output metrics, are only examples and should not be considered as requirements or recommendations for the type of validation to complete.

The scope of this appendix is limited to finite element analysis (FEA). FDA acknowledges that there are other types of computational modeling modalities that can be used to evaluate the mechanics and kinematics of medical devices. Additionally, FDA acknowledges the issues and considerations for non-finite element analyses are similar to those raised for FEA and aspects of this guidance might be applicable. However, there might be aspects of the non-FEA modalities that are distinct from FEA and might present other issues which are not addressed in this appendix but should be included in the reporting of those studies.

Outline of the Report

In the following section, we provide an outline for reporting the details of your computational modeling and simulation study.

I. Executive Report Summary

We recommend that you provide a concise, high-level overview of the entire report including the following:

- Briefly summarize the purpose and scope of the analysis, as well as the rationale for choosing the modeling approach as opposed to other approaches (e.g., experiment).
- Briefly summarize the type(s) of analysis(es) conducted in the computational modeling study (e.g., stress or strain analysis).
- Briefly summarize the model, including geometry, material properties, and boundary conditions.
- If the device has multiple sizes and/or configurations, provide a rationale for the sizes and configurations of the device system evaluated and not evaluated.

- State whether the analysis code/software is commercially available, open source, or user developed.
- Discuss the simulation results (and experimental validation) and their implications for device safety and effectiveness. If applicable, discuss the simulation results with respect to bench testing results.
- Summarize the limitations.
- Summarize the conclusion(s).
- Keywords - please provide up to five keywords or key phrases that describe the modeling modality, the device product code, any relevant materials of the device analysis type, and if applicable, location in the body for intended use (e.g., finite element analysis, MIH, nitinol, fatigue safety factors, aorta). For example, the following are keywords relevant to this subject matter that can be used:
    - finite element analysis, stress analysis, strain analysis, safety factors, fatigue.

II. Background/Introduction

Discuss the purpose and scope of the analysis, as this will dictate the relevant details necessary for review. We recommend that you give a brief device description along with its intended use environment, deployment/implantation procedure, and patient population. The details provided in this section should correspond to the objectives of your analysis.

III. System Geometry (System Configuration)

We recommend that you provide information regarding the geometry of the device, the computational domain, or the modeled *in vitro* test.

A. Details

We recommend that you provide details regarding the device and/or tissue geometry that was modeled and the method used to create the computational representation of your geometry. This section might include CAD drawings or reconstructed digital images.

B. Assumptions, simplifications, and rationale

If you did not model the entire device, describe and provide a rationale for the portion of the device that was modeled (e.g., utilized symmetry). If the device is available in different sizes or configurations, describe which sizes or configurations were modeled and provide a rationale to support the analysis of those sizes. If your device and/or tissue has unique geometric features that might affect the analysis (e.g., surface topography) then describe how those were or were not accounted for in the model. Finally, regarding the method of construction, please include relevant information on limitations and assumptions (e.g., image resolution and smoothing) as related to the geometry.

IV. Constitutive Laws

We recommend that you provide details for all of the constitutive laws or material models used to describe the mechanical behavior of the device material(s) and, if appropriate, the surrounding biological cells/tissues/organs.

A. Details

Describe the stress-strain relationship (e.g., linear, hyperelastic, elastic-plastic, viscoelastic, poroelastic) of the device and/or tissue material(s). Specify the degree of anisotropy (e.g., isotropic, orthotropic) of the material(s). If appropriate, the constitutive relationships should be presented graphically and/or with equations.

Additionally, we recommend that you discuss any material non-linearities that were included in the model. For example, if the model includes plastic deformation, then we recommend that you explain the equations describing the evolution of plasticity (e.g., rate dependence, hardening) in the material. If cyclic loading was modeled, we recommend that you outline the rules governing progressive material damage (fatigue) and/or the loss of material. We recommend that you also specify any additional non-linearities, such as time-dependent behavior and superelasticity. The numerical inputs for the parameters within the constitutive model should be provided in the material properties section.

B. Assumptions, simplifications, and rationale

We recommend that you provide a rationale for the constitutive model you chose to represent the material behavior, and discuss why the assumptions of that constitutive framework are consistent with the material behavior relevant to the computational analysis. For example, if you employed linear, isotropic models, then only homogeneous, small-strain deformations should be presented, and plasticity should only be excluded if stresses in the material remain below the yield strength. We recommend that you validate the constitutive model to confirm that it adequately replicates the experimental behavior of the material and that it is implemented correctly in the computational model.

V. Material Properties (System Properties)

We recommend that you provide details regarding the material properties for the device, and if appropriate, tissue materials used in the analysis. This could include synthetic materials (e.g., stainless steel, titanium, alumina, PMMA, PLGA) and biologic materials (e.g., collagen, arterial tissue, bone, muscle, cartilage, liver).

A. Details

For each material, please provide the material inputs necessary to fully characterize the relevant mechanical behavior of the material. Some examples of important material inputs include:

- Material law coefficients
- Elastic modulus
- Ultimate tensile strength

- Fatigue life/ endurance limit
- Plateau stresses and elastic strain limits for shape memory or superelastic materials such as Nitinol
- Strain at break
- Viscoelastic properties

The inputs for the device material(s) should represent the properties of the material(s) of the final, sterilized device unless an appropriate rationale is provided. The inputs for surrounding biological materials should capture the important aspects of tissue physiology (e.g., healthy versus diseased, young versus mature). Due to the substantial variability in material properties of biological materials, we recommend that you provide a rationale for the selection of properties and describe how the variability of the properties was accounted for in the computational study.

We recommend that you discuss and provide the source for the material inputs. If the values were taken from literature, we recommend that you reference and discuss the publications. If the inputs were obtained from *ex vivo* or *in vitro* testing, provide a description of the testing, including details of the test type (e.g., uniaxial tension, 3-point bend, creep), sample condition (e.g., geometry, processing, heat treatment), protocol (e.g., loading rate, frequency, mean strain), environment (e.g., temperature, humidity, solution), and, if necessary, the method(s) used to compute the material properties from the test data. The device materials used in the testing should represent the finished product, to the extent possible, while biological materials should be taken from, or comparable to, those in the target patient population, unless rationale is provided. The testing should be conducted in an environment that reflects the in-use conditions. For material properties that were determined from *in vivo* tests or data collection (e.g., imaging, implanted sensors), we recommend that you describe the sample population, test methods, the equipment used to gather data, and post-processing performed to extract relevant material inputs.

B. Assumptions, simplifications, and rationale

We recommend that you provide a rationale for the sources of material inputs, and state any assumptions or limitations that were inherent from the sources you cited or the testing that you conducted. For example, we recommend that you discuss why inputs derived from tests conducted in water at room temperature would be as appropriate as results that were derived from testing in physiologic temperature and fluid. Finally, we recommend that you provide the numerical inputs for the parameters of the constitutive model in this section.

VI. Boundary & Initial Conditions (System Conditions)

We recommend that you provide information regarding the conditions that were imposed on the system. These might include, but are not limited to, the boundary and loading conditions, initial conditions, and other constraints that control the system.

A. Details

We recommend that you provide a complete description of the loading conditions that are imposed on the model. Please provide the step-by-step structural analysis procedure that represents the complete stress/strain history of the device. Examples include, but are not limited to, stresses/strains from manufacturing (residual), implantation, and physiologic/pathologic loading. For each analysis step, we recommend the following:

- Provide an overall schematic or diagram that clearly depicts the location and direction of the imposed boundary conditions.
- Specify the three-dimensional magnitude and direction of the applied displacements, forces, pressures, and moments.
- Describe any constraints used in the model, including the location(s) and the degrees of freedom for each fixed or free constraint.
- Provide supporting rationale that describes how each boundary condition (e.g., displacement, force, pressure, moment, constraint) represents the intended loading scenario. Some examples of loading modes include radial dilatation, torsion, bending, axial tension/compression, and temperature.
- Describe the sources and/or methods used to obtain the loading mode and magnitude (e.g., literature data, standards, imaging, other analytic methods).
- Explain how the components are expected to interact. We recommend that you provide a detailed description of the interaction (i.e., contact) between the device and other components within the model, as well as those components that self-contact (e.g., stent struts under axial compression). Describe and provide a rationale for the implementation of contact conditions in the model (e.g., frictionless, coefficient of friction, bonded).

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for all boundary and initial conditions and clearly state any assumptions and simplifications that were made.

VII. Mesh (System Discretization)

We recommend that you provide the following details regarding generation of the mesh.

- Please provide the name (including version number) of the software used to create the mesh.
- Specify the number/density of elements used in the mesh, including any mesh refinement or adaptive meshing in transition regions or regions of complex geometry. You can also include the number of nodes in the model. We recommend that you provide figures depicting the mesh at relevant scales, especially in transition regions or regions of complex geometry and regions of high stress or strain.
- State the type of element(s) selected and discuss why the selected element(s) are appropriate for the analysis performed.
- Provide details of the mesh refinement or convergence analysis to demonstrate that the results are independent of element size.

   - Report on the number of mesh densities used to demonstrate convergence stability of the results with respect to element size.
   - Report the results of the mesh refinement analysis in graphical or tabular format and clearly identify and justify the mesh chosen for subsequent analysis.

VIII. Solver (Numerical Implementation)

We recommend that you provide the following details regarding the software used in the numerical implementation of the analysis.

- Provide the name (including version number) of the software used to solve the model(s).
- If using custom or non-commercial code, provide information on its verification.
- If subroutines are used, provide information on verification (e.g., test case) and details of implementation.
- Describe the type of analysis completed (e.g., static structural, vibration, buckling).
- Provide details on the solver routine used including, at a minimum, the following parameters:
   - State whether the solver is implicit or explicit. If it is explicit, include the analysis time frame and the density. If it is implicit, indicate the step size and/or step increment parameters.
   - Indicate if the solver accounted for nonlinear geometric changes.
   - State the convergence criteria and iteration method.

IX. Post-Processing & Results

We recommend that you provided the following for each analysis step:

- List and provide a rationale for the stress or strain measure(s) reported (e.g., component, principal, von Mises).
- State whether the stresses or strains were reported from integration points or nodes.
- Provide a plot of the critical stresses or strains on a material stress-strain curve to illustrate the material response being modeled (e.g., loading or unloading curve of a superelastic material). Alternately, provide specific values and a rationale for why this plot is not needed (e.g., linear elastic loading curve).
- If applicable, provide a contact map which depicts the interactions between contact surfaces and discuss the results.

We recommend that you provide the following for monotonic loading:

- State and provide a rationale for the failure criterion (e.g., Maximum Shear Stress, Mohr-Coulomb) and provide a graphic or equation that clearly demonstrates how factors of safety were calculated.
- Provide the values and graphically display the location(s) of critical stresses, strains, forces, or displacements.
- For reporting safety factors:

  - Provide a table that specifies the safety factors for each case (i.e., device size, loading mode(s), and analysis step).
  - Show locations of minimum safety factor(s) on the device graphically.

We recommend that you provide the following for fatigue evaluation:

- Describe the method used to calculate mean and alternating stresses/strains (e.g., scalar, tensor).
- State whether cyclic loading results in rotations of the principal directions.
- Graphically display the location(s) of critical mean and alternating stresses or strains.
- State the fatigue criterion (e.g., Goodman, Soderberg) and provide a graphic or equation that clearly demonstrates how fatigue factors of safety are calculated.
- For reporting fatigue safety factors:
  - Provide a table that specifies the critical mean and alternating stresses/strains and the resulting safety factors for each device size, loading mode(s), and analysis step.
  - Show locations of minimum safety factor(s) on the device graphically.
  - Plot mean and/or alternating stress/strains on a point cloud graph and include fatigue criterion if applicable.

For other analysis types (e.g., vibration or buckling) we recommend that you provide all relevant results including critical stresses or strains and their locations on the device as well as describe any post-processing techniques used to evaluate safety and/or performance.

If multiple loading modes were modeled separately, we recommend that you provide a rationale and discuss the implications of superposition of stress or strain states for each loading mode (e.g., location, direction, and phase of the critical stresses or strains).

X. Validation

We recommend that you provide information regarding the methods employed to validate the computational model [1]. Validation of the device or device-tissue model establishes the level of accuracy and predictability of the model and defines the limitations of the model. The results of a validation study serve to support your choice of constitutive relationship, material properties, meshing, and contact. We suggest the following format for presenting that information.

A. Scope

Present the scope and goal of your model validation study. The type of validation study performed and the output metrics compared are at your discretion, but should align with the ultimate goal of your device or device-tissue computational modeling study. Specify the type of information that can be gained from the validation experiment and its relationship to model predictions and accuracy.

B. Methods

Describe the comparator (e.g., physical test, *in vivo*, literature) used for the model validation study. Include information and rationale for the following items:

- mode of loading chosen;
- boundary and loading conditions including the loading and unloading path, as applicable;
- environmental parameters within the experiment (e.g., temperature, humidity); and
- any manufacturing processes or pre-conditioning applied to the device prior to conducting the experiment. For example, if the model is designed to predict safety of a nitinol cardiovascular stent, specify if the device was crimped and if it was tracked through a representative anatomy prior to experimental measurements.

Describe the measuring equipment used to capture data during the experiment and its level of accuracy. For example, if the validation study compares uniaxial force-extension data between the model and an experiment, present the capacity of the load cell used to capture force data and its accuracy.

Describe the locations on the device or tissue where the experimental measurements were acquired. For example, if your study is designed to analyze strain in a hip stem, describe where strain gauges were placed to acquire the data.

Describe the computational model that was used for comparison to experimental data. Specify computational model parameters used for the validation study such as mesh density, element type, and constitutive relationships. If the validation model parameters are different from those used in the device or device-tissue model, provide an appropriate rationale for their differences.

Describe the boundary and loading conditions used for the model and describe how they relate to the validation experiment. For example, the rate and magnitude of applied torsion to a pedicle screw system in the computational model should match that applied to the device mounted on a mechanical testing system.

Describe the computational model output. If applicable, describe any post-processing calculations done to arrive at your output. Please also specify if the output was calculated for the entire system (e.g., reaction force/torque) or if it is calculated in a specific location (e.g., angle of flare in a proximal stent on an endovascular graft).

C. Assumptions and Rationale

List and discuss the assumptions for the computational model of the validation experiment (i.e., neglecting viscous behavior if you are comparing instantaneous force values).

List and discuss the simplifications for the computational model of the validation experiment. These simplifications may be geometric, such as the employment of axisymmetry in the computational model or may consist of explanations for testing device sub-components (e.g., validating the wear scar on articulating components in a total disc replacement device may not necessitate modeling of the device-bone interface).

D. Validation Study Results

Present a comparison of your computational model output and experimental results. For example, if your validation study compared the radial force generated in a stent during crimping, it might be more insightful to compare this force at several diameters between nominal and crimped rather than at the crimped diameter alone.

If applicable, present the percentage difference between your experimental result and computational model.

Include images that directly compare model and experimental results (e.g., deformation or stress contours) as these will provide a qualitative assessment that the model is able to capture relevant behavior. This comparison is likely to be useful for large deformation problems and capturing device behavior under extreme loading conditions.

E. Discussion

Provide a discussion of the extent to which your validation model is able to capture the observed validation experimental behavior.

Include in the discussion the relevance of the validation experiment to expected clinical loading conditions, implications of model and experimental assumptions on the results, limitations on the agreement between the validation model and experiment, and the extent of predictability to the device or device-tissue model.

XI. Limitations

We recommend that you discuss the limitations of the model, which might include, but are not restricted to the following:

- Material properties
- Model geometry
- Boundary conditions
- Biological processes
- Microstructure
- Process conditions (e.g., porous coating).

We recommend that you describe the assumptions and/or simplifications noted previously and how they affect the results and interpretation as they relate to the device.

If the conclusions of the analysis are significantly dependent on the assumptions and/or simplifications in the model, we recommend that you report on a sensitivity analysis of the parameters associated with those assumptions and/or simplifications.

XII. Discussion/Conclusion

We recommend that you discuss the results in the context of the modeling objectives and their implications on device performance and patient safety. For example, discuss how critical stresses or strains obtained from the computational model relate to failure locations observed in bench testing and/or the potential consequences of failure at locations of minimum safety factor. Additionally, we recommend that you address the following points:

- Discuss any inconsistencies between the modeling results and the modeling assumptions and simplifications.
- Discuss the sensitivity of the results to variations in modeling parameters (e.g., material properties, boundary conditions, geometry).

State the overall conclusions of the computational modeling study and whether the objective(s) have been met.

Bibliography

[1] ASME V&V10-2006, Guide for Verification and Validation in Computational Solid Mechanics

Subject Matter Appendix III – Computational Electromagnetics and Optics

For questions regarding this appendix, contact Leonardo Angelone, Ph.D., (301) 796-2595, leonardo.angelone@fda.hhs.gov, for computational electromagnetics or Quanzeng Wang, Ph.D., (301)796-2612, quanzeng.wang@fda.hhs.gov, for computational optics.

Introduction/Scope of the Appendix

The purpose of this appendix is to provide recommendations to industry on the formatting, organization, and content of the reports for computational electromagnetic (EM) and optical modeling and simulation studies used in medical device regulatory submissions to assess (1) safety (e.g., energy deposition, temperature rise, voltages, and thermal damage induced in the human body by medical devices using EM/optical energy) and (2) performance (e.g., how internal or external EM/optical sources and physical properties of devices and tissue affect the performance of medical devices.)

Examples of such studies include safety and performance evaluation of the following medical devices: electrophysiology monitoring devices, magnetic resonance imaging (MRI) systems, MR conditional passive or active implanted devices (e.g., orthopedic devices, stents, pacemakers, and neurostimulators), devices for radiofrequency ablation, optical coherence tomograph devices, fluorescence spectroscopy devices, laser surgery devices, and optical therapy devices.

Outline of the Report

In the following section, we provide an outline for reporting the details of your computational modeling and simulation study.

I. Executive Report Summary

We recommend that you provide a concise and complete overview of the report of the computational modeling and simulation study that includes the following:

- Purpose of the study, including any relevance/correlation to other studies (e.g., bench, clinical) for validation purposes
- Type of the analysis (e.g., photobiological safety, MRI safety, spectroscopy device penetration depth)
- Scope of the analysis (e.g., for a device that has multiple sizes or configurations, discuss what sizes or configurations were modeled, and how the computational model and simulation relates to the intended patient population)

- Conclusions with respect to the study purpose and how they relate to the regulatory submission.
- Keywords - please provide up to five keywords or key phrases that describe the modeling modality, the device product code, any relevant materials of the device analysis type, and if applicable, location in the body for intended use (e.g., radiofrequency dosimetry, OQG, cobalt chromium, magnetic resonance safety, hip). The following are sample keywords relevant to this subject matter that can be used:
    - electrophysiology, radiofrequency, optical imaging, magnetic resonance imaging, active implants, Monte Carlo simulation, and finite difference time domain.

II. Background/Introduction

We recommend that you provide a brief description of the device system and intended use environment. Describe the purpose of the analysis, as this will dictate the relevant details necessary for review. Introduce the background and principles of the model and simulation, and provide a rationale for why it is appropriate to apply the model to the device system.

III. System Geometry (System Configuration)

We recommend that you provide information regarding the device and tissue geometry that was modeled (e.g., the geometry of the device, the computational domain, the *in vivo* or *in vitro* test that is modeled).

A. Details

Describe the components of the system (e.g., device, *in vivo* or *in vitro* environment) to be evaluated. Include images, diagrams (with appropriate scaling bar or dimensions), and a brief description of the model.

Describe the methods (e.g., image reconstruction, computer aided design) used to generate the system configuration and discuss how the configuration was captured appropriately for the intended analysis. If image reconstruction was used to generate geometry, describe the imaging modality.

Describe the software used to generate the system configuration (e.g., computer aided design software, image segmentation software) and describe the methods used to verify the software.

Describe the geometrical characteristics necessary for a comprehensive description of the methodology.

Because there are different applications of computational EM and optical modeling, we have provided the following examples.

1. For EM simulations in MRI environment, please describe:

- the geometrical and physical characteristics of the radiofrequency coils (e.g., geometrical dimensions, number of rungs, number of sources, lumped elements used, if any);
- the physical characteristics of the phantom/anatomical models (e.g., size, dimensions, and body composition) used in the simulations and their clinical significance with respect to the indications of use;
- the landmark positions of the phantom/anatomical models with respect to the coil and their clinical significance;
- the geometrical and physical characteristics of the device (e.g., material properties, path of the implant inside anatomical model) and their clinical significance.

2. For optical simulations, please describe:
   - Geometry of the light source, including the distance and angle between the light source and tissue surface, the beam size, and beam intensity profile (e.g., Gaussian beam). Describe whether and how the illumination takes into consideration of specific optical components, such as fiber optic probes, lenses or mirrors.
   - Geometry of the detector, including spatial and angular restrictions on detected light, as well as the justification for these restrictions (or lack of restrictions).
   - Geometry of the simulated tissue (e.g., size of simulated region, surface morphology, and tissue structures such as layers, vessels, tumors or cysts) and the rationale for implementation of this geometry (e.g., tissue types represented, layers or structures present, and simulated conditions such as normal, metaplastic or neoplastic tissue).

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications used to generate the system configuration as compared to the actual device, tissue object and environment. If appropriate, provide clinical rationale for the *in vivo*/*in vitro* models (e.g., size, disease state, mathematical convenience versus clinical relevance).

IV. Governing Equations/Constitutive Laws

We recommend that you provide information regarding the governing equations and/or constitutive laws used to perform the computational analysis.

A. Details

Provide the governing equations/constitutive laws for the system.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications of the governing equations (e.g., Laplace, Maxwell, Radiative Transport) or constitutive laws chosen to represent the system. If a thermal analysis is included, please report the results as recommended in the Heat Transfer Appendix.

V. System Properties

We recommend that you provide information regarding the biological, chemical, and physical properties of the system.

A. Details

Provide the parameters used in the analysis that define the material and/or process characteristics, and their variability, if applicable. These might include properties of biological materials (e.g., cells, tissues, organs), non-biological materials (device components, implants, contrast agents), and/or processes (e.g., cell signals), such as states (e.g., diseased, healthy), biological properties, chemical properties, and physical properties.

Specifically please provide the following inputs, when appropriate for your simulation.

1. For EM simulations,
   Provide electrical properties of the device (e.g., conductivity, permittivity), the tissue (e.g., conductivity, permittivity, anisotropy), and any relevant, non-biological materials (e.g., air, water, high-dielectric pads surrounding the body).
2. For optical simulations,
   - Provide optical properties of the device (e.g., refractive index of probe surface, numerical aperture, beam convergence or divergence, focal spot size), the tissue or non-tissue object (e.g., absorption coefficient, scattering coefficient, refractive index, scattering anisotropy, quantum yield for fluorescence), and any relevant, non-biological materials (e.g., contrast agents, nanoparticles), along with their variation in space and time (e.g., different tissue components, dynamic changes due to temperature or hydration);
   - Describe any simplifications of the optical properties (e.g., phase function) for the tissue and any relevant, non-biological materials (probes, nanoparticle or dye-based contrast agents) and state whether a diffusion condition was assumed;
   - Provide the key properties of the optical radiation simulated, including the spectral distribution of irradiance, total energy and/or power, spatial intensity distribution, and angular illumination distributions;
   - State whether or not coherence, polarization and fluorescence were considered.
3. For simulations that also include thermal analysis,
   - Provide the physical properties of the object (tissues and non-tissue) used for the simulations (e.g., mass density, thermal conductivity, capacitance, blood perfusion rate, Arrhenius thermal damage coefficients, electrical conductivity and permittivity);
   - Specify any non-linear or coupling between EM/optical and thermal properties of the object.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications used to determine the system properties. Identify the source of biological, chemical, and physical properties (e.g., literature, *in vivo*, *in vitro* testing).

For example, describe the variation of the object material (tissue or non-tissue) properties with position, direction, time, wavelength, light intensity, temperature, and thermal damage. Please describe any non-linearity of material properties incorporated in the model and whether they may affect the modeling results. Please specify whether the system properties are spatially symmetric and steady over time. Please provide a rationale for the use of the physical properties and coefficients adopted. If the properties are derived from literature data, please provide a copy of the publications and discuss their applicability to the specific study. If the properties are derived from bench testing, please provide a full and comprehensive report of the test. Please describe the sensitivity of outcome results on key parameters and provide a systematic analysis of data uncertainty in relation to system properties.

VI. System Conditions

We recommend that you provide information regarding the conditions that were imposed on the system. These might include, but are not limited to, the boundary and loading conditions, initial conditions, and other constraints that control the system.

A. Details

Describe the system conditions imposed on the model and their variability, if applicable. If appropriate, provide a graphical representation of the conditions, depicting how they are applied to the system.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications used to determine the conditions applied on the system. Provide appropriate documentation (e.g., literature, test reports, clinical data, medical imaging data) to support the system conditions.

Specifically, state whether the boundary conditions of the simulations represent a true physical boundary. Please provide evidence demonstrating that boundary conditions do not cause the simulation to generate non-physical results. Moreover, where relevant, describe how the physical properties of surrounding materials between device and tissue (e.g., air, water) will affect the boundary conditions and how the boundary condition will in turn affect the simulation results.

For simulations of optical systems with the purpose of calculating light intensity or energy delivered to human tissue, please provide information on all the assumptions made to model each optical element. For example, light intensity or energy attenuated by each optical element due to reflection, absorption, and scattering at certain wavelength or incident angle, should be specified to properly obtain light intensity and energy delivered to the human tissue.

VII. System Discretization

We recommend that you provide information regarding the discretization and refinement techniques applied to the system for solving it numerically.

A. Details

Describe the system discretization methods and how they were applied to the computational domain. Describe the methodology (e.g., mesh refinement study) used to verify proper numerical discretization. If applicable, provide a representative image of the discretization in the areas of interest of the computational domain. Report the criteria used to determine that the discretization was sufficient to resolve the physics of interest.

B. Assumptions, simplifications and rationale

Describe and provide a rationale for the assumptions and simplifications used to discretize the computational domain.

VIII. Numerical Implementation

We recommend that you provide information regarding the numerical implementation strategy that yielded the solution to the governing equations.

A. Details

Describe the numerical implementation methodology (e.g., boundary element method, finite difference time domain, methods of moments, finite element method, and Monte Carlo simulation) and numerical solver employed to yield the solution to the governing equation. Explain the verification process used to ensure the governing equations were solved correctly. State the solver parameters (e.g., tolerance, relaxation) and convergence criteria, and describe any stability criteria required. For integral models (e.g., Arrhenius equation), discuss the method of numerical integration.

B. Assumptions, simplifications and rationale

Describe and provide a rationale for the assumptions and simplifications used to choose the solver and associated parameters. Specifically, please provide a rationale demonstrating that the parameters selected are sufficient to achieve a convergent solution, specify the convergence criteria and describe why it was appropriate (e.g., time-steps used for finite difference time domain; simulation stopping criteria such as number of photons for Monte Carlo simulation).

IX. Validation

We recommend that you provide information regarding the methods employed to validate the computational model [1].

A. Details

Describe the method used to assess the accuracy of the computational model (e.g., *in vivo* or *in vitro* comparator). Provide sufficient details that describe how the measurements were taken from the comparator and used to assess the accuracy of the predicted numerical output. For example, validation for RF simulations in MRI may be conducted with respect to B_1 field, validation for optical modeling might be conducted with respect to detected light intensity, and validation for optical/thermal or radiofrequency/thermal modeling might be conducted with respect to temperature or thermal damage. Please demonstrate that the error level provides sufficient accuracy for the given application. If an analytical closed-form equation is used to support the validation, please provide the source of the equation.

B. Assumptions, simplifications and rationale

Describe and provide a rationale for the assumptions and simplifications of the method used to validate the computational model. Explain the difference between the measured and predicted value, and discuss its significance with respect to the purpose of the analysis.

X. Results

We recommend that you present the quantitative results from the computational modeling study. Provide the results with sufficient level of details, including labels and legends. The results may be presented in more than one format (e.g., tables, graphs, plots).

XI. Discussion

We recommend that you discuss how the results relate to the purpose of the computational modeling study and the clinical relevance, if appropriate, and how the results compare with the experimental and literature results.

XII. Limitations

We recommend that you provide details regarding (1) how the assumptions and simplifications described in the previous sections might affect the output of the computational model and simulation, (2) the interpretation of the results, and (3) the relevance to the purpose of the study. Describe the outcomes and implications of all the available uncertainty analyses performed on the system properties and conditions.

XIII. Conclusions

We recommend that you summarize the computational study with respect to the purpose of the study and how it relates to the regulatory submission.

Bibliography

[1] IEEE 1597.1-2008 - IEEE Standard for Validation of Computational Electromagnetics Computer Modeling and Simulations

Subject Matter Appendix IV – Computational Ultrasound

For questions regarding this appendix, contact Joshua Soneson, Ph.D., (301) 796-2512 and joshua.soneson@fda.hhs.gov.

Introduction/Scope of the Appendix

The purpose of this appendix is to provide recommendations on the formatting, organization, and content of reports for studies in computational ultrasound in support of device submissions.

Outline of the Report

In the following section, we provide an outline for reporting the details of your computational modeling and simulation study.

I. Executive Report Summary

We recommend that you provide a concise, high-level overview of the assumptions and rationale for the methodology/modeling approach, and the following:

- Describe the type(s) of analysis(es) conducted in the computational modeling study (e.g., wave propagation, heat transfer, fluid flow, thermal dose)
- Describe the purpose of analysis, and in particular, describe any relevance/correlation to bench testing for validation purposes
- State whether the analysis software is open-source, commercial, or developed in-house
- Keywords - please provide up to five keywords or key phrases that describe the modeling modality, the device product code, any relevant materials of the device, analysis type, and if applicable, location in the body for intended use (e.g., finite difference method, KZK, ultrasound, hystotripsy, prostate). For example, the following are sample keywords relevant to this subject matter that can be used:
    - imaging, cavitation, therapeutic ultrasound, histotripsy, acoustic radiation force impulse, Sommerfeld integral, Rayleigh integral, Westervelt, KZK.

II. Background/Introduction

We recommend that you provide a brief device description along with its intended use environment, deployment/implantation procedure and patient population. Additionally, describe the purpose and scope of the analysis, as this will dictate the relevant details necessary for review. The details provided in this section should correspond to the objectives of your analysis.

III. System Geometry (System Configuration)

We recommend that you provide details regarding the device and/or tissue geometry that was modeled. The configuration defines the geometry of the device, computational domain and the anatomical structure included within the computational domain.

A. Details

Describe the components of the system (e.g., device, *in vivo* and/or *in vitro* environment) to be evaluated.

Regarding the ultrasound source, include images, diagrams (with appropriate scaling bar or dimensions), and a brief description of the model(s). Specifically, discuss whether the ultrasound source is a spherical bowl or phased-array transducer. If the latter, state how many elements and how are they arranged. Finally, provide the dimensions of the device and its geometry.

Regarding the anatomy, describe the methods (e.g., image reconstruction) used to generate the simulated anatomy and discuss the techniques used to demonstrate that the configuration was captured appropriately for the intended analysis, if applicable. For example, if bone is included in the computational domain, describe how it was modeled. If blood vessel are included in the computational domain, describe the blood vessels that were modeled and represented (e.g., statistically versus simulating a single representative geometry). Finally, describe any scaling or similarities used in the modeling approach.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications used to generate the system configuration as compared to the actual device and environment. If the entire device system was not modeled or if simplifications were made to the geometry, then provide a rationale for the system geometry that was analyzed (e.g., use of symmetry). Describe the difference between the model and the real situation as it pertains to the purpose of the computational modeling study. For example, if bones are present, describe if the shear-wave propagation (and subsequent heating due shear-wave absorption) was modeled. Additionally, as manufacturing tolerances can affect device functionality, describe how the range of design and manufacturing tolerance dimensions influence the results compared to nominal dimensions.

IV. Governing Equations

We recommend that you provide information regarding the governing equations used to perform the computational analysis.

A. Details

Describe the basic equations used in the simulation. Specifically, state whether the propagation model is full-wave or parabolic, and linear or nonlinear. If acoustic streaming, mechanical, and/or thermal effects are included, discuss the coupling of the system.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications of the basic mathematical equations that were implemented for the model and simulation, specifically regarding the type of propagation model employed.

V. System Properties

We recommend that you provide, preferably in tabular format, all physical properties, coefficients, descriptive equations used in the simulation and post processing.

A. Details

We have provided the following as an example of how to report the system properties.

Tissue properties

Property	**Numerical value**	**Unit**
Small signal sound speed		
Mass density		
Absorption		
Coefficient of nonlinearity		
Heat capacity		
Thermal conductivity		
Perfusion rate		

Transducer characteristics

Characteristic	**Numerical value**	**Unit**
Acoustic power		
Frequency		
Pressure/phase distribution		

We recommend that you indicate the dependence of properties on other variables, such as temperature, frequency, thermal dose and location, if included.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications used to determine the system properties. Identify the sources of the physical properties and coefficients adopted (e.g., literature, *in vivo*, *ex vivo*, *in vitro* testing).

If literature data are cited and the data are condition-specific, discuss their applicability to the model. If testing is conducted to determine the parameters, describe the test methods and results as applicable to the model.

If there are uncertainties associated with the data (i.e., due to accuracies, simplifications, or variations), you should perform a sensitivity analysis, if appropriate, to address the effect of the uncertainties on the simulation results.

VI. Boundary & Initial Conditions (System Conditions)

We recommend that you provide a complete description of the initial and boundary conditions that are imposed on the model. These include, but are not limited to, absorbing boundaries and transducer loading. Provide a rationale for the choice of the initial/boundary conditions and if appropriate, provide a graphical representation of the conditions, depicting how they are applied to the system.

VII. System Discretization

We recommend that you provide the following details regarding the spatial discretization.

A. Details

Describe the spatial discretization method and, if applicable, the technique used to integrate the evolution variable. If complex geometry requires the use of a non-uniform mesh, provide images/diagrams of the mesh. Additionally, indicate the details of the mesh. Specifically,

- describe and provide a rationale for the quality of the mesh (e.g., element/cell types, sizes, shapes, quality metrics (e.g., aspect ratios) and formulations chosen for the production mesh for the mesh of the analysis domain); and.
- discuss mesh refinement in areas of interest, for example, where the field changes rapidly in space.

If adaptive meshing refinement techniques were employed, then discuss the methods and provide details regarding the finished mesh.

B. Assumptions, simplifications and rationale

Describe and provide a rationale for the assumptions and simplifications used to discretize the computational domain and, if applicable, the integration scheme. Perform a convergence analysis (solution as a function of mesh density) and provide details that demonstrate that discretization adequately resolved the physics of interest.

VIII. Numerical Implementation

We recommend that you provide the following details regarding the software used in the numerical implementation of the analysis. For models using differential equations, discuss the method used to solve the discrete equations. For integral models, discuss the method of numerical integration. Provide a rationale for the choice of the methods used and possible effects on the solution. Finally, describe and provide a rationale for any techniques used to accelerate the computation, such as neglecting terms in regions where they have subleading order, adaptive stepping or variable number of harmonics.

IX. Validation

We recommend that you provide information regarding the methods employed to validate the computational model. Specifically, describe the method(s) used to assess the accuracy of the computational model with appropriate bench methods, conserved quantities and known analytical solutions. Provide diagrams and data to support the assessment of the model. Provide details on how the measurements were taken from the bench test and compared to the computational model. Discuss any differences between bench testing/known solutions and results from the computational model.

X. Results

We recommend that you present the quantitative results from the computational modeling study over the range of intended use parameters. Provide the results with a sufficient level of details, including labels and legends. The results may be presented in more than one format (e.g., table, graph, plot).

XI. Discussion

We recommend that you discuss how the results relate to the purpose of the computational modeling study, and if appropriate the clinical relevance and how the results compare with experimental and literature results, if these results exist.

XII. Limitations

Describe the assumptions/simplifications made in the model generation, simulation and analysis. Discuss how those assumptions/simplifications might affect the output of the model and the interpretation of its relevance to the device and safety. Describe the outcomes and implications of all the available uncertainty analyses performed on the system properties and conditions.

XIII. Conclusions

We recommend that you summarize the computational study with respect to the purpose of the study and how it relates to the regulatory submission.

Subject Matter Appendix V – Computational Heat Transfer

For questions regarding this appendix, contact Joshua Soneson, Ph.D., (301) 796-2512 and joshua.soneson@fda.hhs.gov.

Introduction/Scope of the Appendix

The purpose of this appendix is to provide recommendations on the formatting, organization, and content of reports for studies in computational heat transfer in support of device submissions.

Outline of the Report

In the following section, we provide an outline for reporting the details of your computational modeling and simulation study.

I. Executive Report Summary

We recommend that you provide a concise, high-level overview of the assumptions and rationale for the methodology/modeling approach, and the following:

- Describe the type(s) of analysis(es) conducted in the computational modeling study (e.g., radiation or conduction heat transfer, fluid flow, chemical reaction, EM or acoustic absorption)
- Describe the purpose of analysis, and in particular, describe any relevance/correlation to bench testing for validation purposes
- State whether the analysis software is open-source, commercial, or developed in-house
- Keywords - please provide up to five keywords or key phrases that describe the modeling modality, the device product code, any relevant materials of the device, analysis type, and if applicable, location in the body for intended use (e.g., finite difference method, MNB, heat conduction, thermal ablation, uterus). For example, the following are sample keywords relevant to this subject matter that can be used:
  - thermal diffusivity, source, diffusion equation, heat capacity, radiation, conduction.

II. Background/Introduction

We recommend that you provide a brief device description along with its intended use environment, deployment/implantation procedure and patient population. Additionally, describe the purpose and scope of the analysis, as this will dictate the relevant details necessary for review. The details provided in this section should correspond to the objectives of your analysis.

III. System Geometry (System Configuration)

We recommend that you provide details regarding the device and/or tissue geometry that was modeled. The configuration defines the geometry of the device, computational domain and the anatomical structure included within the computational domain.

A. Details

Describe the components of the system (e.g., device, *in vivo* and/or *in vitro* environment) to be evaluated.

Regarding the heat source, include images, diagrams (with appropriate scaling bar or dimensions) and a brief description of the model(s). Additionally, provide dimensions of device and geometry.

Regarding the anatomy, describe the methods (e.g., image reconstruction) used to generate the simulated anatomy and discuss the techniques used to demonstrate that the configuration was captured appropriately for the intended analysis, if applicable. Finally, describe any scaling or similarities used in the modeling approach.

Describe the methods for quantifying temperature-induced bioeffects such as phase change or thermal damage.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications used to generate the system configuration as compared to the actual device and environment. If the entire device system was not modeled or if simplifications were made to the geometry, then provide a rationale for the system geometry that was analyzed (e.g., use of symmetry). Describe the difference between the model and the real situation as it pertains to the purpose of the computational modeling study. Additionally, as manufacturing tolerances can affect device functionality, describe how the range of design and manufacturing tolerance dimensions influence the results compared to nominal dimensions.

IV. Governing Equations

We recommend that you provide information regarding the governing equations used to perform the computational analysis.

A. Details

Describe the basic equations used in the simulation. Specifically, state whether materials are isotropic and if not, describe how anisotropy is addressed. Describe the coupling to other physical processes (i.e., fluid flow, heat sources in domain or on boundary) that were included in the model.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications of the basic mathematical equations that were implemented for the model and simulation, as well as the methods for quantifying thermal damage.

V. System Properties

We recommend that you provide, preferably in tabular format, all physical properties, coefficients and descriptive equations used in the simulation and post processing.

A. Details

We have provided the following as an example of how to report the system properties.

Tissue properties

Property	Numerical value	Unit
Mass density		
Heat capacity		
Thermal conductivity		
Perfusion rate		

We recommend that you indicate the dependence of properties on other variables, such as temperature, frequency, thermal damage and location, if included.

B. Assumptions, simplifications, and rationale

Describe and provide a rationale for the assumptions and simplifications used to determine the system properties. Identify the sources of the physical properties and coefficients adopted (e.g., literature, in vivo, ex vivo, in vitro testing).

If literature data are cited and the data are condition specific, discuss their applicability to the model. If testing is conducted to determine the parameters, describe the test methods and results as applicable to the model.

If there are uncertainties associated with the data (i.e., due to accuracies, simplifications or variations), perform sensitivity analysis, if appropriate, to address the effect of the uncertainties on the simulation results.

VI. Boundary & Initial Conditions (System Conditions)

We recommend that you provide a complete description of the initial and boundary conditions that are imposed on the model. Provide a rationale for the choice of the initial/boundary conditions and if appropriate, provide a graphical representation of the conditions, depicting how they are applied to the system.

VII. System Discretization

We recommend that you provide the following details regarding the spatial discretization.

A. Details

Describe the spatial discretization method and, if applicable, the technique used to integrate the evolution variable. If complex geometry requires the use of a non-uniform mesh, provide images/diagrams of the mesh. Additionally, indicate the details of the mesh. Specifically, you should:

- describe and provide a rationale for the quality of the mesh (e.g., element/cell types, sizes, shapes, quality metrics (e.g., aspect ratios) and formulations chosen for the production mesh for the mesh of the analysis domain); and.
- discuss mesh refinement in areas of interest, for example, where the field changes rapidly in space.

If adaptive meshing refinement techniques were employed, then discuss the methods and provide details regarding the finished mesh.

B. Assumptions, simplifications and rationale

Describe and provide a rationale for the assumptions and simplifications used to discretize the computational domain and, if applicable, the integration scheme. Perform a convergence analysis (solution as a function of mesh density), a stability analysis where applicable, and provide details that demonstrate that the discretization adequately resolved the physics of interest.

VIII. Numerical Implementation

We recommend that you provide the following details regarding the software used in the numerical implementation of the analysis. For models using differential equations, discuss the method used to solve the discrete equations. For integral models, discuss the method of numerical integration. Provide a rationale for the choice of the methods used and possible effects on the solution. Finally, describe and provide a rationale for any techniques used to accelerate the computation, such as neglecting terms in regions where they have subleading order, adaptive stepping, etc.

IX. Validation

We recommend that you provide information regarding the methods employed to validate the computational model. Specifically, describe the method(s) used to assess the accuracy of the computational model with appropriate bench methods, conserved quantities and known analytical solutions. Provide diagrams and data to support the assessment of the model. Provide details on how the measurements were taken from the bench test and compared to the computational model. Discuss any differences between bench testing/known solutions and results from the computational model.

X. Results

We recommend that you present the quantitative results from the computational modeling study over the range of intended use parameters. Provide the results with sufficient level of details, including labels and legends. The results may be presented in more than one format (e.g., table, graph, plot).

XI. Discussion

We recommend that you discuss how the results relate to the purpose of the computational modeling study, and if appropriate the clinical relevance and how the results compare with experimental and literature results, if these results exist.

XII. Limitations

Describe the assumptions/simplifications made in the model generation, simulation and analysis. Discuss how those assumptions/simplifications might affect the output of the model and the interpretation of its relevance to the device and safety. Describe the outcomes and implications of all the available uncertainty analyses performed on the system properties and conditions.

XIII. Conclusions

We recommend that you summarize the computational study with respect to the purpose of the study and how it relates to the regulatory submission.